REMARKS

Support for new Claim 40 can be found, *inter alia*, in Claim 20 of the present specification. Support for new Claims 41-42 can be found, *inter alia*, at page 11, lines 19 *et seq* of the present specification. Hence, new Claims 40-42 do not constitute new matter, and thus entry is requested.

The Examiner has withdrawn from consideration Claims 37-38 as being directed to non-elected inventions of Group II (canceled Claim 17) and Group III (canceled Claim 18), respectively.

Accordingly, non-elected Claims 37-38 are hereby cancelled without prejudice to the filing of a Divisional Application with respect to the same.

On page 2 of the Office Action, the Examiner rejects Claim 20 under 35 U.S. § 112, second paragraph. Specifically, the Examiner states that in view of the use of the term "comprising" in reference to a compound, the claim is indefinite.

In view of the amendments to Claim 20, i.e., to replace the phrase "...comprising an indole compound according to formula (I):" with "...represented by formula (I):", Applicants respectfully submit that the Examiner's rejection has been rendered moot.

In addition, on pages 2-3 of the Office Action, the Examiner rejects Claims 20-36 and 39 under 35 U.S.C. § 103 over Davis et al (U.S. Patent No. 5,057,614; hereinafter "Davis") or

Barth et al I or II (U.S. Patent Nos. 5,380,746 and 5,516,915; hereinafter "Barth I" and "Barth II").

Specifically, the Examiner states that Davis, Barth I and Barth II disclose homologous, isomeric or analogous compounds that are sufficiently closely related to the claimed compounds as to render them obvious. The Examiner asserts that, absent evidence of unobvious or unexpected properties, the claimed compounds would be expected to have "essentially the same properties" as those taught by the art. The Examiner has not give any weight to the intended use of the claimed compounds as inhibitors of apoptosis or necrosis in making this rejection, on the grounds that the intended use allegedly does not limit the scope of the rejected claims.

For the following reasons, Applicants respectfully traverse the Examiner's rejection.

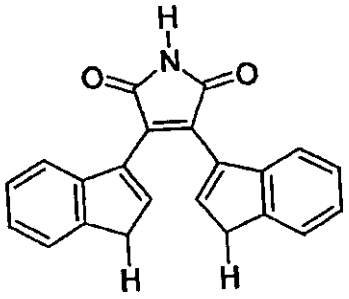
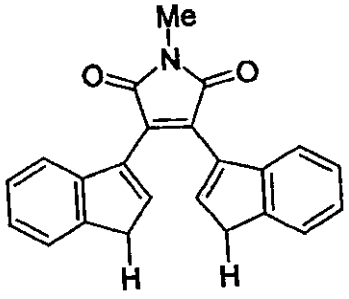
Applicants respectfully submit that the Examiner is incorrect in failing to considering the intended use of the claimed compounds in making his rejection. A rejection for obviousness may be made when the chemical compounds of the claims and those of the cited art have very close structural similarities and similar utilities. MPEP 2144.09. The present invention is directed to compounds that are inhibitors of apoptosis or necrosis, while the compounds of the cited references are taught as inhibitors of protein kinase C (see, e.g., Davis at column 11, lines 25-41, and Barth I and II at columns 1, lines 22-25). Thus, Applicants respectfully submit that the Examiner has not established a *prima facie* case of obviousness because the compounds of the present claims and

those taught by the cited references have quite different utilities (see, the present specification at page 7, first full paragraph).

More specifically, as discussed at page 7, lines 9 up to page 8, line 6 of the present specification, cell death inhibiting activity is quite different from protein kinase C (PKC) inhibiting activity.

In Toullec et al, *J. Biol. Chem.*, 266:15771-15781 (1991) (hereinafter referred to as "Toullec et al"), a copy of which is attached hereto, inhibition of PKC is shown in Table I on page 15772.

INHIBITION OF PROTEIN KINASE C BY BISINDOLYL COMPOUNDS

no.	structure	IC_{50} (μM)
3		0.01 ± 0.05
4		> 50

The above Compound Nos. 3 and 4 correspond to Compounds 13 and 14, respectively, in Table 3 at page 37 of the present

application. As shown above, Compound 13 is a potent PKC inhibitor, whereas Compound 14 does not significantly inhibit PKC. Accordingly, since PKC inhibiting activity does not predictably correspond to cell death inhibiting activity, the compounds of the present invention, which all having the cell death inhibiting activity, cannot be predicted from the cited references.

In particular, Barth I and Barth II teach the use of bisindolylmaleimide for the treatment of vascular diseases, such as thrombosis, arterial sclerosis, and hypertension, etc., for the treatment of inflammatory processes, allergy, cancer and certain degenerative injury in the central nervous system, and for the treatment of diseases of the immune system and virus diseases. However, only one example is given as real test examples, showing inhibitory activities against some protein kinases and it is short of reasonable evidence demonstrating effectiveness in treating the enumerated diseases. Barth I and Barth II have no evidence for the causal and effect relationship between the above diseases and the activities inhibitory against PKC. Moreover, the present invention is concerned with drugs that inhibit cell death and their uses and is totally far from the concept of preexisting PKC inhibitors represented by Barth I and Barth II.

As to Davis, this reference teaches the use of bisindolylmaleimide for the treatment of acquired immune deficiency via the inhibition of HIV transfection and for the treatment of cardio-vascular diseases via their inhibitory effects on the contraction of smooth muscle cells. In fact, however, the test examples only show inhibitory activity for PKC, and thus it

is short of reasonable evidence for the effectiveness on these disorders. Furthermore, the present invention does not describe the inhibition of HIV infection, but describes the inhibitory effect on cell death, and thus possesses conceptually different actions and different situations of use. In addition, regarding cardio-vascular diseases, the present is invention concerned with therapeutic drugs that involve the inhibition of cell death in cardiac cells which may occur during ischemia or under other various conditions. These therapeutic drugs are conceptually different from pre-existing drugs which merely improve vascular circulation through vascular dilatation.

In any event, the Examiner is requested to note that in the cited references, all of the final products have -NH at the position of X in formula (I) of the present invention. In new dependent Claim 40, for the definition N-R^5, R≠H, i.e., -NH of the cited references, is not claimed.

Accordingly, Applicants respectfully submit that the present invention is not taught or suggested by Davis, Barth I or Barth II, and thus request withdrawal of the Examiner's rejection.

In view of the amendments to the claims, and the arguments set forth above, reexamination, reconsideration and allowance are respectfully requested.

The Examiner is invited to contact the undersigned at his Washington telephone number on any questions which might arise.

Respectfully submitted,

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A P P E N D I X

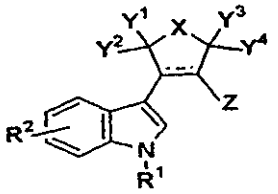
Marked-Up Version of to Show Changes

IN THE CLAIMS:

Claims 37 and 38 are being cancelled.

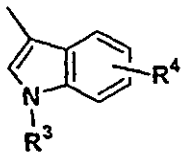
Claim 20 is being amended as follows:

Claim 20. (Amended) An inhibitor of apoptosis or necrosis [comprising an indole compound according to] represented by formula (I):



(I)

wherein X represents an oxygen atom or N-R^5; Z represents a halogen atom or



R^1 and R^3 each independently represents a hydrogen atom, an alkyl group which is substituted or unsubstituted, an alkenyl group which is substituted or unsubstituted, an alkynyl group which is substituted or unsubstituted, an aryl group which is substituted or unsubstituted, an acyl group which is substituted or unsubstituted, an alkoxy- or aryloxycarbonyl group which is substituted or unsubstituted, an alkyl- or arylthiocarbonyl group which is substituted or unsubstituted, an aminocarbonyl group which is substituted or unsubstituted, an alkyl- or

arylsulfonyl group which is substituted or unsubstituted, an alkoxyl group or an aryloxy group which is substituted or unsubstituted, or a hydroxyl group; R^2 and R^4 each represents substituent(s) on an indole ring, in which number and position (2-, 4-, 5-, 6-, or 7-position as position number of the indole ring) of the substituent(s) and kinds of the substituent(s) may be the same or different, and represents a hydrogen atom, an alkyl group which is substituted or unsubstituted, an alkenyl group which is substituted or unsubstituted, an alkynyl group which is substituted or unsubstituted, an aryl group which is substituted or unsubstituted, an acyl group which is substituted or unsubstituted, an alkoxy- or aryloxycarbonyl group which is substituted or unsubstituted, an alkyl- or arylthiocarbonyl group which is substituted or unsubstituted, an aminocarbonyl group which is substituted or unsubstituted, an alkyl- or arylsulfonyl group which is substituted or unsubstituted, an alkoxyl group or an aryloxy group which is substituted or unsubstituted, an alkyl- or arylthio group which is substituted or unsubstituted, a hydroxyl group, a carboxyl group, a cyano group, a nitro group, an amino group which is substituted or unsubstituted, or a halogen atom; R^5 represents an alkyl group which is substituted or unsubstituted, an alkenyl group which is substituted or unsubstituted, an alkynyl group which is substituted or unsubstituted, an aryl group which is substituted or unsubstituted, an alkoxyl group or an aryloxy group which is substituted or unsubstituted, an amino group which is substituted or unsubstituted, a hydroxyl group, or a hydrogen atom; Y^1 and Y^2, and Y^3 and Y^4 each independently represent two hydrogen atoms or a hydrogen atom and a hydroxyl group, or are combined to form a carbonyl group; and R^1 and R^2, R^1 and R^3, R^3

and R^4, or R^2 and R^4 may be combined to form a hydrocarbon chain or a hydrocarbon chain containing hetero atom(s) which is substituted or unsubstituted; and in the formula, the bond accompanying a dotted line represents a double bond or a single bond, or a pharmaceutically acceptable salt thereof.

New Claims 40-42 are being added